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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/071,541	05/04/1998	H.-J. SU HUANG	040750-5001	5607

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EXAMINER	
MAIER, LEIGH C	
ART UNIT	**PAPER NUMBER**
1623	

DATE MAILED: 03/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/071,541	HUANG ET AL.	
	Examiner	Art Unit	
	Leigh C. Maier	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

In view of the Appeal Brief filed on November 26, 2003, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 6, 7, and 9-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Tsai et al (Cancer Res., 1996) with Garcia de Palazzo et al (Cancer Res., 1993) to support inherency.

Tsai discloses treatment of NSCLC cells with a combination of cisplatin and tyrphostin AG825. See abstract. The reference is silent with regard to the presence of a mutant EGFR gene.

However, as admitted by Applicant (see specification, p. 3, 2nd full paragraph – lung cancer generically) and taught by de Palazzo (see abstract – NSCLC specifically) mutant EGFR genes (type III, ΔEGFR) are expressed in many cases of lung cancer. Treatment of such cells with the required combination of therapeutic agents would inherently accomplish the method, regardless of whether or not this was recognized by the reference.

Since the Office does not have the facilities for preparing the claimed materials and comparing them with prior art inventions, the burden is on Applicant to show a novel or unobvious difference between the claimed product and the product of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980).

With regard to "an effective amount" of the TK inhibitor and other therapeutic agent, Applicant admits that there is no criticality in the amounts used, suggesting amounts known in the art. See specification, p. 18, lines 4-15.

Further regarding the selectivity of the TK inhibitor, applicant's definition of "relatively selective" appears to be a measurable increase in affinity of the inhibitor for the mutant EGFR gene over the wt. Again, the Office is not able to make this determination in the Tsai procedure.

In the description of the methods, Tsai discloses the protocol for administering the therapeutic agents. See p. 1069, paragraph beginning "Anticancer Agents and Tyrphostin AG825." Each is dissolved separately and then mixed. Before mixing the separate agents comprise a "kit." After mixing they comprise a "pharmaceutical composition."

Claims 1-3, 6, 7, and 9-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Kufe et al (US 6,524,832).

Kufe discloses the killing of tumor cells via apoptosis comprising the administration of DNA-damaging agents, such as cisplatin, in combination with TK inhibitors. See col 4, lines 55-60 and col 5, lines 23-45. The reference exemplifies treatment of HL-60 cells with cisplatin and genistein. See example 1. The reference further teaches the preparation of kits and pharmaceutical compositions to carry out this method of treatment. See col 6, lines 1-12. The matter of effective amounts has been addressed above.

The reference is silent with regard to the presence of a mutant EGFR gene. However, as admitted by Applicant (see specification, p. 3, 2nd full paragraph – cancer generically), mutant EGFR genes, such as ΔEGFR, are expressed in many types of cancer. Treatment of such cells with the required combination of therapeutic agents would inherently accomplish the method, regardless of whether or not this was recognized by the reference.

Since the Office does not have the facilities for preparing the claimed materials and comparing them with prior art inventions, the burden is on Applicant to show a novel or unobvious difference between the claimed product and the product of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nagane et al (Cancer Res., 1996) and Han et al (Cancer Res., 1996) in view of Kondo et al (Cancer Res., 1995).

The invention is drawn to a method of modulating inhibition of apoptosis in a target cell or tissue of a mutant EGFR gene by administering an effective amount of a TK inhibitor to the cell or tissue, in combination with a therapy that is effective to induce apoptosis or increase the rate of apoptosis. The mutant gene may be ΔEGFR. The cell/tissue may be a tumor selected from the group consisting of glioma, breast cancer, lung cancer, and ovarian cancer. Other therapeutic agents may be cisplatin, paclitaxel, or vincristine. The TK inhibitor may be tyrphostin AG1478. Also claimed are kits and pharmaceutical compositions for use in said method.

Nagane teaches that expression of ΔEGFR enhances tumorigenicity and inhibits apoptosis. See abstract. The reference does not teach the administration of a TK inhibitor or any agent that induces/increases apoptosis.

Han teaches that AG1478 specifically inhibits the TK activity of ΔEGFR over wt EGFR. See last paragraph and p. 3860, rt col. The reference specifically suggests the use of AG1478 for the treatment of tumors expressing ΔEGFR, including glioma, lung, breast, and cancers of the gynecological system. See p. 3861, beginning at the paragraph bridging the columns and continuing through the end of the reference. The reference does not teach administration in combination with another therapeutic agent that induces/increases apoptosis.

The apoptosis-inducing agent, cisplatin, is known for the treatment of malignant glioma. See Kondo, abstract and first paragraph of reference.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to administer a TK inhibitor, such as AG1478, to a tumor cell expressing mutant EGFR gene, wherein the TK inhibitor is relatively selective for the particular gene to modulate the apoptosis-inhibiting effect in said cell. One of ordinary skill would be motivated to effect such treatment in order to reverse the apoptosis inhibiting effect of the mutant EGFR with a reasonable expectation of success. It would be further obvious to co-administer an apoptosis-inducing agent, such as cisplatin, for the additive effects. (The showing of synergistic effects will be addressed hereinbelow. See "Allowable Subject Matter.")

It would be within the scope of the artisan to select amounts known in the art for said treatment. As discussed above, there has been no demonstration of criticality in the amounts

used. It would be further obvious to prepare pharmaceutical compositions and kits to be used for the method.

Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nagane et al (Cancer Res., 1996) and Han et al (Cancer Res., 1996) in view of Kondo et al (Cancer Res., 1995) and further in view of Howell et al (US 5,597,798).

The invention is as set forth above.

Nagane, Han, and Kondo teach as set forth above. The references do not teach the full scope of cancer types or therapeutic agents.

Howell teaches that cisplatin, as well as other agents, such as taxol (paclitaxel) are known for the treatment of several types of cancer, including ovarian, lung, breast, and malignant glioma. See, for example, col 3, lines 12-55.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to use any therapeutic agent known for the treatment of the cancers taught by Han in combination with a selective tyrphostin in the method discussed above for the additive effects. Effective amounts, pharmaceutical compositions, and kits have been addressed above.

Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kufe et al (US 6,524,832) in view of Wagner et al (Int. J. Cancer, 1996) and Han et al (Cancer Res., 1996).

The invention is as set forth above.

Kufe teaches as set forth above. The reference further teaches the use of tyrphostins as the TK inhibitor. See col 20, lines 16-27. The reference also specifically suggests the treatment

of other cancers, such as pancreas and breast. See col 18, line 60, continuing through col 19, line 7. The reference does not exemplify the treatment of the recited cancers with the recited therapeutic agents in combination with tyrphostins, such as AG1478.

Wagner teaches that expression of a truncated EGFR (apparently ΔEGFR) inhibits the apoptotic activity of cisplatin in pancreatic cancer cells. See abstract.

Han teaches as set forth above.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to treat cancer cells, such as pancreatic or breast, with a combination of a TK inhibitor, such as AG1478, and an apoptotis-inducing agent such as cisplatin. Kufe had taught the utility of using these two types of therapeutic agents in combination. Therefore, one of ordinary skill would be motivated to select cisplatin and AG1478 because the former has known utility in the treatment of pancreatic cancer, and AG1478 preferentially inhibits the mutant EGFR known to be expressed in this cancer. One of ordinary skill would reasonably expect success in combining them to modulate apoptosis in these cells.

Allowable Subject Matter

It is the opinion of the examiner that the synergistic effect shown with the combination of a relatively specific TK inhibitor and an apoptosis-inducing/increasing agent constitutes a showing of unexpected results. However, the showing is not commensurate with the scope of the claims. For example, claim 1 does not require a selective TK inhibitor (selective for the particular mutant expressed in the cell/tissue being treated), whereas Applicant admits that "non-specific and less potent tyrphostins . . . had no effect on apoptosis induction . . ." and suggests

that a selective tyrphostin is necessary for synergistic effect. See specification, p. 26, lines 3-9. Although Kufe alludes to a synergistic effect in using these types of agents in combination, (see col 4, lines 30-36) the results by Applicant (no synergy with non-selective tyrphostins) undercut this proposed synergy for the generic combination. Applicant has demonstrated that not all TK inhibitors in combination with an apoptosis-inducing agent provides a synergistic effect, but that a measure of selectivity is necessary.

Possible avenues for amending the claims will depend on what, if any, mutant EGFR is expressed in the Tsai (or Kufe) cells and how selective AG825 (or genistein) is for said mutant (if present):

(1) If the Tsai (or Kufe) cells comprise no mutant EGFR, or if it is present, but AG825 (or genistein) is not selective for it, amending claims 1, 9, and 13 to require that the TK inhibitor be "relative selective" for the particular mutant comprised in the cell/tissue being treated would put the claims in order for allowance.

(2) If the Tsai (or Kufe) cells *do* comprise a mutant EGFR *and* AG825 (or genistein) is relatively selective for said mutant, amending the claims as in the preceding paragraph and limiting the TK inhibitor to AG1478 would put the claims in order for allowance.

Examiner's hours, phone & fax numbers

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leigh Maier whose telephone number is (571) 272-0656. The examiner can normally be reached on Tuesday, Wednesday, and Friday 7:00 to 3:30 (ET).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson (571) 272-0661, may be contacted. The fax number for Group 1600, Art Unit 1623 is (703) 308-4556 or 305-3592.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-1235.

Visit the U.S. PTO's site on the World Wide Web at http://**www.uspto.gov**. This site contains lots of valuable information including the latest PTO fees, downloadable forms, basic search capabilities and much more.

Leigh C. Maier
Patent Examiner
March 5, 2004

SAMUEL BARTS
PRIMARY EXAMINER
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